Lipid Profile and Subsequent Cardiovascular Disease among Young Adults Aged < 50 Years

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Epidemiological evidence on the relationship between lipid profile and cardiovascular disease (CVD) events in young adults remains insufficient. Thus, we sought to explore the association of lipid profile with subsequent CVD among young adults. Medical records of 1,451,997 young adults (20 to 49 years old) without prior history of CVD and not taking lipid lowering medications were extracted from the Japan Medical Data Center, a nationwide epidemiological database. We conducted multivariable Cox regression analyses to identify the association between lipid profile and the subsequent risk of CVD and used multiple imputation for missing data on body mass index, waist circumference, hypertension, diabetes mellitus, and cigarette smoking in our database. The mean age was 39.0 ± 7.4 years, and 58.5% were men. After a mean follow-up of 1,148 ± 893 days, myocardial infarction, angina pectoris, stroke, and heart failure developed in 1,638 (0.1%), 15,887 (1.1%), 5,593 (0.4%), and 14,351 (1.0%) subjects, respectively. Multivariable Cox regression analyses including covariates after multiple imputation for missing values demonstrated that LDL-C ≥ 140 mg/dL, HDL-C < 40 mg/dL, and triglycerides ≥ 150 mg/dL were independently associated with the incidence of myocardial infarction, angina pectoris, and heart failure. However, they were not associated with the incidence of stroke. Multivariable Cox regression analyses including the number of abnormal lipid profiles and covariates showed that the incidence of myocardial infarction, angina, and heart failure increased stepwise with the number of abnormal lipid profiles. However, the number of abnormal lipid profiles was not associated with the subsequent risk of stroke. In conclusion, the comprehensive analysis of a nationwide epidemiological database demonstrated a close relationship between lipid profile and subsequent CVD, suggesting the importance of maintaining an optimal lipid profile for the primary prevention of CVD in young generations. **(Am J Cardiol 2021;142:59−65)**

Cardiovascular disease (CVD) is a major cause of death and morbidity, and lipid profile plays a pivotal role in the development of CVD.[1,2] Currently, the importance of CVD prevention in young adults is increasingly recognized because epidemiological data show that trends in CVD incidence in young adults have been increasing more or stagnating compared with the older population.[3-6] For example, it was reported that dyslipidemia was one of the most common modifiable risk factors among > 1 million young adults suffering from myocardial infarction in the United States.[7] Therefore, the optimal risk stratification and timely management of dyslipidemia are necessary for the primary prevention of CVD among young adults. In this study, we sought to explore the relationship of lipid profiles with future CVD in young adults without prevalent CVD using a nationwide epidemiological database.

Methods

This retrospective observational study analysed data from the health claims database of the Japan Medical Data Center (JMDC, Tokyo, Japan).[8,9] The JMDC contracts with more than 60 insurers and includes data for health insurance claims on insured patients who are mostly employees of relatively large Japanese companies, with more than 5 million patients registered in it. Incidence of CVD events such as myocardial infarction, angina pectoris, stroke, and heart failure from each individual's claim records was evaluated using the International Classification of Disease, 10th Revision (ICD-10) diagnosis codes. ICD-10 codes used in this study are summarized in the Supplementary Material. Each CVD event was analyzed separately. For example, if a participant had myocardial infarction and then had heart failure

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See page 64 for disclosure information.

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Table 1
Characteristics of study population

Variables	Missing	(n = 1,451,997)
Age (years)	0	39.0 ± 7.4
20-29	0	205,858 (14.2%)
30-39	0	360,655 (24.8%)
40-49	0	885,484 (61.0%)
Men	0	848,735 (58.5%)
Body Mass Index (kg/m^2)	669 (0.05)	22.6 ± 3.8
Obesity	669 (0.05)	319,167 (22.0%)
Waist Circumference (cm)	142,209 (9.8)	79.9 ± 10.1
High Waist Circumference	142,209 (9.8)	322,510 (24.6%)
Hypertension	1,166 (0.08)	141,811 (9.8)
Systolic Blood Pressure (mm Hg)	1,167 (0.08)	116 ± 15
Diastolic Blood Pressure (mm Hg)	1,167 (0.08)	71 ± 11
Diabetes Mellitus	287,614 (19.8)	23,295 (2.0%)
Cigarette Smoker	13,829 (1.0)	400,151 (27.8%)
Laboratory Data		
Low-density lipoprotein cholesterol (mg/dL)	0	115 ± 31
High-density lipoprotein cholesterol (mg/dL)	0	63 ± 16
Triglycerides (mg/dL)	0	101 ± 84
Low-density lipoprotein cholesterol ≥ 140 mg/dL	0	298,491 (20.6%)
High-density lipoprotein cholesterol < 40 mg/dL	0	64,580 (4.4%)
Triglycerides ≥ 150 mg/dL	0	223,858 (15.4%)
Number of Abnormal Lipid Profile		
0	0	999,931 (68.9%)
1	0	329,238 (22.7%)
2	0	110,793 (7.6%)
3	0	12,035 (0.8%)
Glucose (mg/dL)	289,704 (20.0)	91 ± 14
HbA1c (%)	253,042 (17.4)	5.4 ± 0.5

Data are expressed as mean ± standard deviation or number (percentage).

a month later, both myocardial infarction and heart failure events were counted as separate outcomes.

We included subjects who did not take any lipid-lowering medications and whose heath check-up data at baseline were available for assessing lipid profile and enrolled in the JMDC database between January 2005 and August 2018. Exclusion criteria were as follows: (1) age < 20 years, (2) age ≥50 years, and (3) prior history of myocardial infarction, angina pectoris, coronary revascularization, stroke, heart failure, and hemodialysis.

This study was approved by the Ethical Committee of The University of Tokyo (2018-10862) and is in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived because all data in the JMDC database were anonymised.

Using the blood test data at the initial health check-up, abnormal lipid profile was defined as low-density lipoprotein-cholesterol (LDL-C) ≥ 140 mg/dL, high-density lipoprotein-cholesterol (HDL-C) < 40 mg/dL, or triglycerides ≥ 150 mg/dL. Obesity was defined as body mass index of ≥ 25 kg/m^2. High waist circumference was defined as waist circumference ≥ 85 cm for men and waist circumference ≥ 90 cm for women.[9] Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mm Hg, or use of anti-hypertensive medications. Diabetes mellitus was defined as fasting glucose level ≥ 126 mg/dL or use of antidiabetic medications.

Categorical and continuous data are presented as numbers (%) and mean ± standard deviation. We conducted multivariable Cox regression analyses to identify the association between lipid profile and the subsequent risk of CVD. There were missing data on body mass index, waist circumference, hypertension, diabetes mellitus, and cigarette smoking as shown in Table 1. Hence, we used multiple imputation to replace those missing values with other plausible values by creating multiple filling-in patterns as previously described.[8] Here, we replaced each missing value with a set of substituted plausible values by creating 20 filled-in complete data sets using a multiple imputation by chained equation method. Covariates included in the multivariable Cox regression analysis were used in the multiple imputation process. In other words, all variables in the analysis model were included in the imputation model. Hazard ratio and standard errors were obtained using Rubin's rules. We also performed the multivariable Cox regression analysis in subjects without missing values (complete case analysis). The Kaplan−Meier curves and log-rank test were used to assess the significance of differences in the incidence of CVD between the numbers of abnormal lipid profiles. p value < 0.05 was considered statistically significant. We performed all statistical analyses using SPSS software (SPSS version 25, SPSS Inc., Chicago, Illinois) and STATA (STATA version 16, StataCorp LLC, College Station, Texas).

Results

From 2,289,422 subjects extracted from the JMDC database, we excluded patients who were aged < 20 years

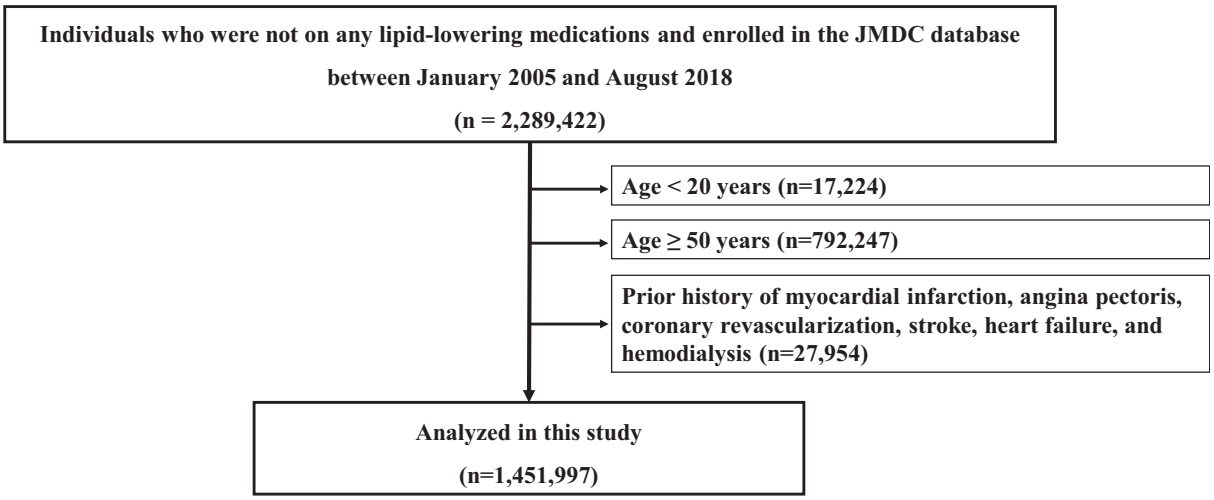


Figure 1. Flowchart.

(n = 17,224), ≥50 years (n = 792,247), with prior history of myocardial infarction, angina pectoris, coronary revascularization, stroke, heart failure, and haemodialysis (n = 27,954). Finally, we analysed 1,451,997 subjects in this study (Figure 1).

Clinical characteristics of the study population are shown in Table 1. The mean age was 39.0 ± 7.4 years, and 848,735 subjects (58.5%) were men. The mean follow-up period was 1,148 ± 893 days. Mean LDL-C, HDL-C, and triglyceride values were 115 ± 31 mg/dL, 63 ± 16 mg/dL, and 101 ± 84 mg/dL, respectively. Approximately 30% of the study population had at least one abnormal lipid profile at baseline, and multiple abnormal lipid profiles were observed in 122,828 patients (8.5%).

During the follow-up period, myocardial infarction, angina pectoris, stroke, and heart failure occurred in 1,638 (0.1%), 15,887 (1.1%), 5,593 (0.4%), and 14,351 (1.0%) patients, respectively.

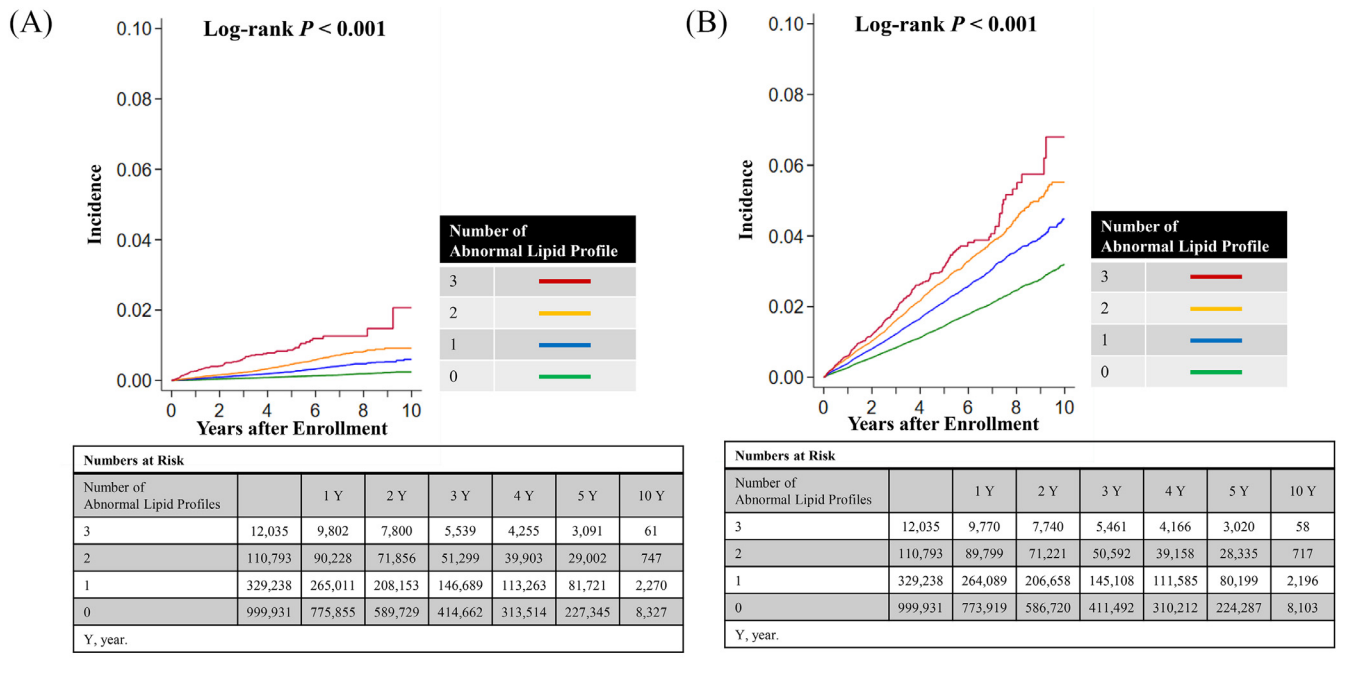
Multivariable Cox regression analysis after multiple imputation for missing values demonstrated that LDL-C ≥ 140 mg/dL, HDL-C < 40 mg/dL, and triglycerides ≥ 150 mg/dL were independently associated with the development of myocardial infarction, angina pectoris, and heart failure, respectively. However, they were not associated with the incidence of stroke (Table 2). Ranges of E values for the observed estimates of association between abnormal lipid profile and incident CVD were between 1.4 and 3.1. Multivariable Cox regression analysis including covariates in subjects without missing values (complete case analysis) confirmed the results (Supplementary Table 1). We assessed the proportional hazards assumptions by graphically checking log-log plots, and obvious violation of the assumption was not found.

Kaplan-Meier curves and the log-rank test showed that the number of abnormal lipid profiles including LDL-C ≥ 140 mg/dL, HDL-C < 40 mg/dL, and triglycerides ≥ 150 mg/dL was associated with development of myocardial infarction, angina pectoris, stroke, and heart failure (Figure 1). Multivariable Cox regression analysis after multiple imputation demonstrated that the incidence of myocardial infarction, angina, and heart failure increased stepwise with the number of abnormal lipid profiles. However, the number of abnormal lipid profiles was not associated with the subsequent risk of stroke in this model (Table 3). Ranges of E values for the observed estimates of association between the number of abnormal lipid profile and incident CVD were between 1.5 and 7.2. Multivariable Cox regression analysis including covariates in subjects without missing values (complete case analysis) confirmed the results (Supplementary Table 2). We assessed the proportional hazards assumptions by graphically checking log-log plots, and obvious violation of the assumption was not found.

Discussion

Recent epidemiologic statistics shows that CVD in young adults is an urgent healthcare issue, and public health measures for CVD prevention are required.[4] Dyslipidemia is one of the most common risk factors for CVD.[1,2] Therefore, exploring the association between lipid profile and the incidence of CVD events among young adults is crucial.

To the best of our knowledge, this is the first large scale study to investigate the association between lipid profile and the incidence of wide-range CVD events in young adults. However, our results are generally in line with preceding studies.[10–13] Klag et al. examined 1,017 young men followed up for approximately 30 years and reported that serum cholesterol level was associated with higher incidences of CVD, coronary heart disease, and CVD-death.[10] Similarly, Stamler et al. analysed 3 cohorts of younger men and also reported that serum cholesterol level was independently associated with subsequent CVD, and CVD-mortality.[11] Zhang et al. analysed data from 6 United States cohorts with observations from young adulthood to later life, and reported that cumulative exposures to LDL-C during young adulthood were associated with increased CVD incidence.[12] Although a largescale clinical evidence on the association of dyslipidemia and CVD among Japanese young adults is not available, Lee et al. very recently analysed a Korean nationwide cohort and reported that the risk of death, myocardial infarction, and stroke were



Numbers at Risk

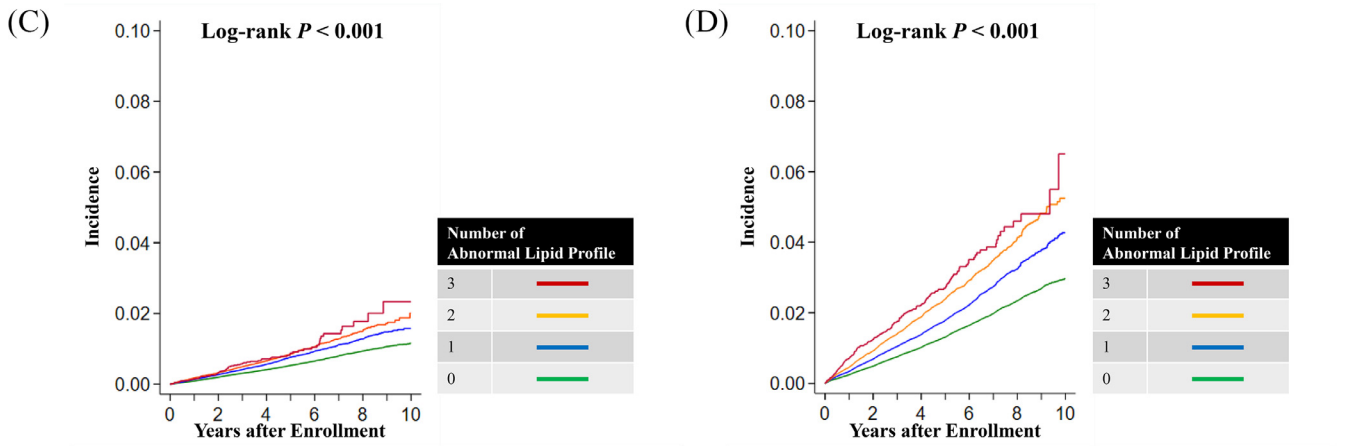
Number of Abnormal Lipid Profiles		1 Y	2 Y	3 Y	4 Y	5 Y	10 Y
3	12,035	9,802	7,800	5,539	4,255	3,091	61
2	110,793	90,228	71,856	51,299	39,903	29,002	747
1	329,238	265,011	208,153	146,689	113,263	81,721	2,270
0	999,931	775,855	589,729	414,662	313,514	227,345	8,327

Y, year.

Numbers at Risk

Number of Abnormal Lipid Profiles		1 Y	2 Y	3 Y	4 Y	5 Y	10 Y
3	12,035	9,770	7,740	5,461	4,166	3,020	58
2	110,793	89,799	71,221	50,592	39,158	28,335	717
1	329,238	264,089	206,658	145,108	111,585	80,199	2,196
0	999,931	773,919	586,720	411,492	310,212	224,287	8,103

Y, year.



Numbers at Risk

Number of Abnormal Lipid Profiles		1 Y	2 Y	3 Y	4 Y	5 Y	10 Y
3	12,035	9,817	7,809	5,542	4,261	3,097	60
2	110,793	90,145	71,737	51,185	39,782	28,905	738
1	329,238	264,765	207,797	146,275	112,829	81,298	2,256
0	999,931	775,338	588,877	413,721	312,533	226,470	8,272

Y, year.

Numbers at Risk

Number of Abnormal Lipid Profiles		1 Y	2 Y	3 Y	4 Y	5 Y	10 Y
3	12,035	9,760	7,732	5,490	4,209	3,050	61
2	110,793	89,909	71,332	59,757	39,345	28,152	726
1	329,238	264,272	206,964	145,468	112,032	80,570	2,217
0	999,931	774,208	587,199	412,029	310,822	224,884	8,155

Y, year.

Figure. 2. Kaplan-Meier Curves: (A) myocardial infarction; (B) angina pectoris; (C) stroke; (D) heart failure.

proportional to lipid levels, positively with total cholesterol and triglyceride levels and negatively with HDL-C level.[14]

The strong relationship between dyslipidemia and the incidence of coronary heart disease was established by preceding studies.[15-17] However, the association between dyslipidemia and the subsequent development of heart failure has not been established yet.[18-20] Our results demonstrated that high LDL-C, low HDL-C, and high triglycerides were all associated with the elevated incidence of heart failure. Given that these components are all associated with the incident coronary heart disease, they may increase ischemic cardiomyopathy and lead to heart failure. Furthermore, triglyceride accumulation in heart muscle tissue could induce lipotoxic cardiomyopathy and cardiac steatosis.[21] Further investigations are required to clarify the underlying pathological mechanism and to establish the optimal preventive strategy for subsequent heart failure through lipid profile management.

Contrary to previous studies,[14,22] high LDL-C, low HDL-C, and high triglycerides were not associated with the incidence of stroke. Although Kaplan-Meier curves showed the statistical significant difference in the incidence of stroke, the difference did not reach statistical significance in the multivariable model. There was no statistical increase in the stroke incidence even in patients with high LDL-C,

Table 2
Multivariable Cox regression analysis after multiple imputation

Variables	Hazard ratio	95% Confidence interval	p Value
Myocardial infarction			
Low-density lipoprotein cholesterol ≥ 140mg/dL	1.83	1.65-2.02	< 0.001
High-density lipoprotein cholesterol < 40mg/dL	1.45	1.24-1.71	< 0.001
Triglycerides ≥ 150mg/dL	1.22	1.09-1.37	0.001
Angina pectoris			
Low-density lipoprotein cholesterol ≥ 140mg/dL	1.15	1.11-1.19	< 0.001
High-density lipoprotein cholesterol < 40mg/dL	1.08	1.01-1.16	0.020
Triglycerides ≥ 150mg/dL	1.14	1.09-1.19	< 0.001
Stroke			
Low-density lipoprotein cholesterol ≥ 140mg/dL	1.04	0.98-1.11	0.195
High-density lipoprotein cholesterol < 40mg/dL	1.07	0.95-1.20	0.248
Triglycerides ≥ 150mg/dL	1.04	0.97-1.12	0.281
Heart failure			
Low-density lipoprotein cholesterol ≥ 140mg/dL	1.09	1.05-1.13	< 0.001
High-density lipoprotein cholesterol < 40mg/dL	1.15	1.07-1.23	< 0.001
Triglycerides ≥ 150mg/dL	1.07	1.02-1.12	0.003

Hazard ratios were adjusted with age, sex, obesity, high waist circumference, hypertension, diabetes mellitus, and cigarette smoking.

low HDL-C, and high triglycerides all combined. Further studies with a longer observational period might be needed to confirm our results.

We believe that our study has several clinical implications. Although most preceding investigations including young adults so far focused on later CVD events such as in 10 to 20 years, results of our study presented that the risk of CVD among young subjects with dyslipidemia might elevate within a few years, which would be much faster than generally expected. Therefore, our results would be informative for the risk stratification of CVD in our clinical settings. Lifestyle modifications are with no doubt important for dyslipidemia. For example, our earlier study confirmed that body weight loss ≥ 5% could ameliorate abnormal lipid profiles among general population.[23] However, achieving the optimal lipid profile control is often not easy by lifestyle modification alone, in our clinical practice. In such cases, considering that there was a difference in the incidence of CVD during the mean follow-up period of approximately 3 years, early pharmacological intervention should also be considered. Since cumulative exposure to dyslipidemia in young adulthood is reported to elevate the future risk of coronary heart disease, the latest guidelines underscore the significance of timely lipid profile screening for young generations.[24,25] In addition, the advantage of the early initiation of lipid-lowering treatment for young adults was reported recently.[26] Hence, we should not hesitate to administer lipid-lowering intervention for young adults. Simultaneously, we also need to acknowledge that the absolute risks of CVD were not so high among young adults. Therefore, it is required to consider the indication of pharmacological intervention for dyslipidemia in young adults from the perspective of cost-effectiveness and health care economics as well.

There are several limitations to this study. We performed multivariable analyses. However, there could be unmeasured confounders and residual bias. Furthermore, E values were relatively low in our analysis, and therefore, we should take the possibility of the influence of unmeasured confounders into consideration more carefully. Although we performed multivariable Cox regression analyses after multiple imputation, the presence of missing values was a major limitation. The data of the JMDC database were mainly obtained from an employed, working-age population. Therefore, healthy worker bias should be acknowledged. Comparing with other epidemiological data in Japan,[27,28] the incidence of CVD in

Table 3
Multivariable Cox regression analysis after multiple imputation

Myocardial infarction

Variables	Hazard ratio	95% Confidence interval	p Value
Number of the abnormal lipid profiles			
0	Reference		
1	1.54	1.37-1.74	< 0.001
2	2.03	1.76-2.34	< 0.001
3	3.88	3.03-4.96	< 0.001

Angina pectoris

Variables	Hazard ratio	95% Confidence interval	p Value
Number of the abnormal lipid profiles			
0	Reference		
1	1.14	1.10-1.19	< 0.001
2	1.28	1.22-1.35	< 0.001
3	1.47	1.30-1.68	< 0.001

Stroke

Variables	Hazard ratio	95% Confidence interval	p Value
Number of the abnormal lipid profiles			
0	Reference		
1	1.05	0.99-1.12	0.120
2	1.08	0.99-1.18	0.092
3	1.18	0.93-1.48	0.167

Heart failure

Variables	Hazard ratio	95% Confidence interval	p Value
Number of the abnormal lipid profiles			
0	Reference		
1	1.06	1.02-1.11	0.002
2	1.18	1.12-1.25	< 0.001
3	1.40	1.23-1.60	< 0.001

Hazard ratios were adjusted with age, sex, obesity, high waist circumference, hypertension, diabetes mellitus, and cigarette smoking.

our study is reasonable. However, recorded diagnoses are generally considered less well validated due to the nature of retrospective design and administrative database (using ICD-10 codes). Data on CVD death were not available in this database. Although we excluded subjects on treatment using lipid-lowering medications at baseline, we had no information on medical treatment during the follow-up which could have influenced the results.

In conclusion, the comprehensive analysis of a nationwide epidemiological database showed that high LDL-C, low HDL-C, and high triglycerides were associated with an elevated risk of CVD such as myocardial infarction, angina pectoris, and heart failure among young adults without prior history of prevalent CVD, suggesting the essential pathological role of dyslipidemia in the development of CVD in young adults.

Disclosures

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors Contribution

*Hidehiro Kaneko: Corresponding author. Conception and design or analysis and interpretation of data. Drafting of the manuscript;

Hidetaka Itoh: Analysis of data;

Hiroyuki Kiriyama: Revising it critically for important intellectual content;

Tatsuya Kamon: Analysis of data;

Katsuhito Fujiu: Revising it critically for important intellectual content;

Kojiro Morita: Analysis and interpretation of data;

Nobuaki Michihata: Analysis and interpretation of data;

Taisuke Jo: Data collection. Analysis and interpretation of data;

Norifumi Takeda: Revising it critically for important intellectual content;

Hiroyuki Morita: Revising it critically for important intellectual content;

Hideo Yasunaga: Conception and design or analysis and interpretation of data. Final approval of the manuscript submitted;

Issei Komuro: Final approval of the manuscript submitted.

Supplementary materials

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